## REMARKS

Claims 22-31 and 49-52 are pending; claims 53-59 are new.

Restriction Requirement

Applicants acknowledge that the Examiner has withdrawn *sua sponte* the restriction requirement mailed 12/18/00.

Telephone Interviews

Applicants wish to thank Examiner Zeman for a telephone interview on October 24, 2001, during which the undersigned and Examiner Zeman discussed C.F.R. and *M.P.E.P.* provisions relating to declaring of an interference when at least one claim was allowable, and further discussed the outstanding rejection under 35 U.S.C. § 112, first paragraph.

Procedure for Declaring an Interference

Applicants have taken note of the statement made at page 2 of the present office action that "[b]efore an interference can be declared, all claims pending in the application must be allowable." Applicants respectfully submit that this position is contrary to the administrative regulations promulgated by the Commissioner and to the guidance provided by the *Manual of Patent Examination Procedure*, 8th ed., which states quite clearly that non-allowed claims may be designated to correspond to the count.

> Note that for each count, every claim in a party's application or patent must be designated as either corresponding or not corresponding to the count; ***this includes any claims of the application which may be under rejection.***

*M.P.E.P.*, 8th ed., August 2001, § 2309.02 (emphasis added).

Pursuant to 37 C.F.R. 1.607(c), Applicants hereby inform the Examiner that one or more of the claims potentially correspond, exactly or substantially, to (a) claims 1, 2, and 4 of U.S. Patent No. 5,998,134, Lee et al., and (b) U.S. Patent No. 5,858,771, Lee et al.

35 U.S.C. § 112, second paragraph

Claims 22, 23, 29, and 49 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite with respect to the terms 'in a mammal,' 'wild-type,' and 'determine.' The rejection is respectfully traversed on all three grounds. The preamble of claims 22 and 23 have been amended to remove the phrase 'in a mammal,' and 'in a human,' and to clarify that the 'cell sample' is a 'mammalian cell sample.' The rejection is traversed with respect to the term 'wild-type RB cDNA probe,' which one of skill in the art in 1986, on reading Applicants' disclosure, would have understood to mean a DNA sequence which is complementary structurally to an RNA transcript of approximately 4.7 kb from the retinal cell line of a human individual who is not affected by retinoblastoma, and which is structurally characterized by the restriction fragment map shown in Fig. 1. Third, Applicants respectfully submit that neither claim 22 nor claim 23 recite the term 'determine.'

Claim 29 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite with respect to the phrase 'normal retinoblastoma protein.' The rejection is respectfully traversed. The specification is prolific in its discussion of the extensive pedigree analysis undertaken when attempting to identify the genetic locus for retinoblastoma. In the context of pedigree analysis, "normal" can be taken to refer to the phenotype of an individual who does not exhibit symptoms associated with retinoblastoma. One of skill in the art in 1986, on reading Applicants' disclosure, would have understood the term "normal" in this context.

35 U.S.C. § 112, first paragraph, Written Description

Claims 24, 26-31, 42, and 50-53 [sic.[1]] have been rejected under 35 U.S.C. § 112, first paragraph, for containing subject matter not described in the specification so as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The rejection is respectfully traversed.

Claim 24 is directed to a nucleic acid that encodes the protein shown in Fig. 6. One of ordinary skill in the art would know that the protein identified and structurally described in Fig. 6 is encoded by one of a finite set of nucleic acids, including the nucleic acid sequence of exons 1-27 shown in Fig. 6 and codon-degenerate variants thereof.

Claim 26, as amended, recites "An isolated nucleic acid molecule that is complementary to a 4.7 kb retinal mRNA, said mRNA being present in a cellular sample isolated from a human who lacks symptoms of retinoblastoma neoplastic disease, wherein said isolated nucleic acid has the restriction fragment map shown in Fig. 1." The restriction fragment map shown in Fig. 1 is a structural characteristic of the claimed subject matter, providing a precise definition of the structural and physical properties of the claimed nucleic acid, so as to permit those skilled in the art to distinguish the subject matter of the claimed genus. *See,* Declaration of Thaddeus P. Dryja, M.D. (submitted herewith unsigned, a signed copy of this Declaration will be provided by subsequent transmittal).

Furthermore, the specification in its entirety provides a written description that would convey to one skilled in the art in 1986 that the inventors were in possession of the subject matter

[1] No claim 53 was pending in the application as of the mailing date of the office action. Thus, the

of claim 26. In particular, the specification states,

> To test this possibility, p7H30.7R was radiolabeled and used to probe a Northern blot of RNA isolated from three retinoblastoma tumors and an adenovirus 12-transformed human embryonic retinal cell line (Vaessen et al., 1986, *EMBO Journal*, Vol. 5, pp. 335-). The p7H30.7R probe hybridized to an RNA transcript of approximately 4.7 kb from the retinal cell line, but did not hybridize to any RNA transcripts from the three tumor samples.
>
> Subsequently, RNA isolated from the adenovirus-transformed retinal cell line was used to construct a cDNA library. This library was screened with the labeled p7H30.7R probe. Several cDNA clones were isolated which had similar restriction maps. The longest of these, p4.7R, contained 4.7 kb of DNA. The restriction map of the insert in the clone p4.7R is shown in Fig. 1.
>
> The p4.7R clone was used to screen RNA transcripts isolated from four retinoblastomas, an osteosarcoma, and the adenovirus-transformed retinal cells. In a Northern blot analysis of isolated RNA's, the p4.7R probe cross-reacted with a 4.7 kb transcript in the transformed retinal cells which was not present in the four retinoblastoma and one osteosarcoma cell samples.

Specification, page 8, line 8, to page 9, line 15. (*See, also,* parent application 06/895,163, at page 5, lines 1-15)

Claim 27, as amended in independent form, is directed to a nucleic acid that encodes the protein shown in Fig. 6. One of ordinary skill in the art would know that such protein is encoded by one of a finite set of nucleic acids, including the nucleic acid sequence of exons 1-27 shown in Fig. 6 and codon-degenerate variants thereof.

Claims 28, 30, and 50: During the telephone interview of October 24, 2001, the Examiner provided guidance that, by amending claim 28 to put it in independent form, the present rejection would be overcome as to claims 28, 30, and 50. Claim 28 has been amended accordingly.

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current rejection is not seen to apply to present claim 53, which is newly added herein.

Claim 29 incorporates the limitations of claim 26 as amended. The specification is clear that the term 'normal' refers to a human patient lacking the symptoms of retinoblastoma.

Claim 30 is directed to a nucleic acid that encodes the protein shown in Fig. 5. One of ordinary skill in the art would know that the protein described in Fig. 5 is encoded by one of a finite set of nucleic acids, including the nucleic acid sequence of Fig. 5 and codon-degenerate variants thereof.

Claim 31 has been amended to depend solely from claim 24, and incorporates the limitations of claim 24, which are discussed above.

Claims 51 and 52: During the telephone interview of October 24, 2001, the Examiner provided guidance that, by amending claim 51 to put it in independent form, the present rejection would be overcome as to claims 51 and 52. Claim 51 has been amended accordingly.

[Claim 53: No claim 53 was pending as of the date of the current office action; Applicants infer that the Examiner intended the present rejection to apply to claims "50-52."]

Obviousness-type Double Patenting

Claims 24-30, 42, and 50-52 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-48 of U.S. Patent No. 5,853,988 ("the '988 patent"). Although the rejection has been met by the terminal disclaimer submitted herewith, Applicants respectfully submit that none of the instant claims are obvious in view of at least claim 18 of the '988 patent. Claim 18 of the '988 patent recites the specific DNA polymorphisms referred to in the specification as RB1.2, RB1.3, RB1.20, and RB1.26.

Claims 22, 23, and 49 have been rejected under the judicially created doctrine of

obviousness-type double patenting as being unpatentable over claims 49-55 of U.S. Patent No. 5,853,988. A terminal disclaimer is submitted herewith for the purpose of overcoming the instant rejection.

Inventorship

Responding to the Examiner's request for clarification concerning the named inventors of the '988 patent and the instant application, Applicants submit that Dr. David Yandell made an inventive contribution to at least claim 18 of the '988 patent. The undersigned is presently of the understanding that Dr. Yandell did not make an inventive contribution to a claim of the instant application, as such claims are currently expressed. In the event that any claim is amended in a manner that is inconsistent with current inventorship designations, applicants will inform the Office and seek appropriate correction.

CONCLUSION

In view of the foregoing, it is submitted that the application is in condition for allowance and such action is respectfully requested. Please charge any fees or apply any credits to our Deposit Account No. 50-1895, Ref. No. 0300-005009.

The undersigned may be reached at 508-428-4000.

Respectfully submitted,

Date: 10/30/01

Leslie Meyer-Leon

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Enclosures: Declaration
Fee Transmittal
Petition for Extension of Time (three months)
Change of Correspondence Address
Terminal Disclaimer
Check ($1030.00)
Postcard

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Version With Markings To Show Changes Made

22 (Twice Amended). A method of detecting a mutated retinoblastoma ("RB") nucleic acid [in a mammal], the method comprising the steps of:

(i) hybridizing an isolated full-length, wild-type RB cDNA probe to a mammalian cell sample; and

(ii) detecting a mutated RB nucleic acid.

23 (Amended). A method of detecting a mutated retinoblastoma ("RB") gene [in a human], the method comprising the steps of:

(i) isolating RNA from a cell sample;

(ii) hybridizing the RNA with an isolated full-length, wild-type RB cDNA probe; and

(iii) detecting the presence of an abnormal RB RNA, the presence of a normal RB RNA or absence of an RB RNA, wherein the presence of an abnormal RB RNA or the absence of an RB RNA indicates a mutated RB gene.

26 (Twice Amended). An isolated nucleic acid molecule [encoding retinoblastoma protein] that is complementary to a 4.7 kb retinal mRNA, said mRNA being present in a cellular sample isolated from a human who lacks symptoms of retinoblastoma neoplastic disease, wherein said isolated nucleic acid has the restriction fragment map shown in FIG. 1.

27 (Twice Amended). [The] An isolated nucleic acid molecule [of claim 26] that encodes a retinoblastoma protein, wherein said retinoblastoma protein has the amino acid sequence [encoded by exons 1-27, inclusive, as] shown in FIG. 6.

28 (Amended). [The] An isolated nucleic acid molecule [of claim 26], wherein said

nucleic acid has an open-reading frame, and wherein the 5' end of said open-reading frame is shown at nucleotide position four of the nucleotide sequence shown in FIG. 5, and the 3' end of said open-reading frame is shown at nucleotide position 2784 of the nucleotide sequence shown in FIG. 5.

31 (Twice Amended). A method of using [a] the nucleic acid of [any one of claims 24-30] claim 24 to express a polypeptide encoded by said nucleic acid, said method comprising the steps of providing said nucleic acid in a cell or in an expression system, and expressing said polypeptide from said nucleic acid.

51 (Amended). [The] An isolated nucleic acid molecule [of claim 26], wherein said nucleic acid has an open-reading frame, and wherein the 5' end of said open-reading frame is shown at nucleotide position 337 of the nucleotide sequence shown in FIG. 5, and the 3' end of said open-reading frame is shown at nucleotide position 2784 of the nucleotide sequence shown in FIG. 5.